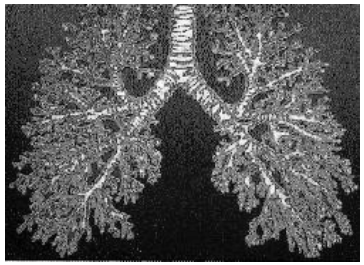

Phénotypes et biomarqueurs de l'asthme

Opportunités thérapeutiques

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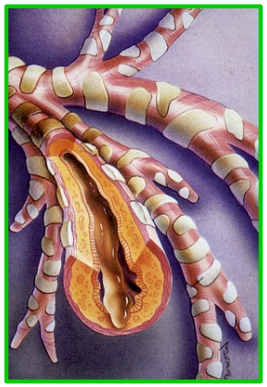
DE CARDIOLOGIE
ET DE PNEUMOLOGIE
DE QUÉBEC

Phénotypes et biomarqueurs de l'asthme - opportunités thérapeutiques



- Le cas du mepolizumab
- Le traitement de l'asthme en 2012
- L'asthme: multiples phénotypes
- Études récentes sur les biomarqueurs
- Que nous réserve le futur
- **Conclusions**

Le cas du mepolizumab

A Study to Evaluate Safety and Efficacy of Mepolizumab in Patients with Moderate Persistent Asthma

Patrick Flood-Page[1], Cheri Swenson[2], Isidore Faiferman[3], John Matthews[3], Michael Williams[3], Lesley Brannick[3], Douglas Robinson[4], Sally Wenzel[5], William Busse[2], Trevor T. Hansel[4], and Neil C. Barnes[6], on behalf of the International Mepolizumab Study Group*

[1]Royal Gwent Hospital, Newport, Wales, United Kingdom; [2]Allergy and Asthma Clinical Research Unit, University of Wisconsin-Madison, Madison, Wisconsin; [3]Respiratory and Inflammation Discovery Medicine, GlaxoSmithKline, Greenford, United Kingdom; [4]National Heart and Lung Institute, Imperial College London, London, United Kingdom; [5]National Jewish Medical and Research Center, Denver, Colorado; and [6]London Chest Hospital, London, United Kingdom

Rationale: Accumulation of eosinophils in the bronchial mucosa of individuals with asthma is considered to be a central event in the pathogenesis of asthma. In animal models, airway eosinophil recruitment and airway hyperresponsiveness in response to allergen challenge are reduced by specific targeting of interleukin-5. A previous small dose-finding study found that mepolizumab, a humanized anti–interleukin-5 monoclonal antibody, had no effect on allergen challenge in humans.

Objectives: To investigate the effect of three intravenous infusions of mepolizumab, 250 or 750 mg at monthly intervals, on clinical outcome measures in 362 patients with asthma experiencing persistent symptoms despite inhaled corticosteroid therapy (400–1,000 μg of beclomethasone or equivalent).

Methods: Multicenter, randomized, double-blind, placebo-controlled study.

Measurements and Main Results: Morning peak expiratory flow, forced expiratory volume in 1 second, daily β_2-agonist use, symptom scores, exacerbation rates, and quality of life measures. Sputum eosinophil levels were also measured in a subgroup of 37 individuals. Mepolizu-

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

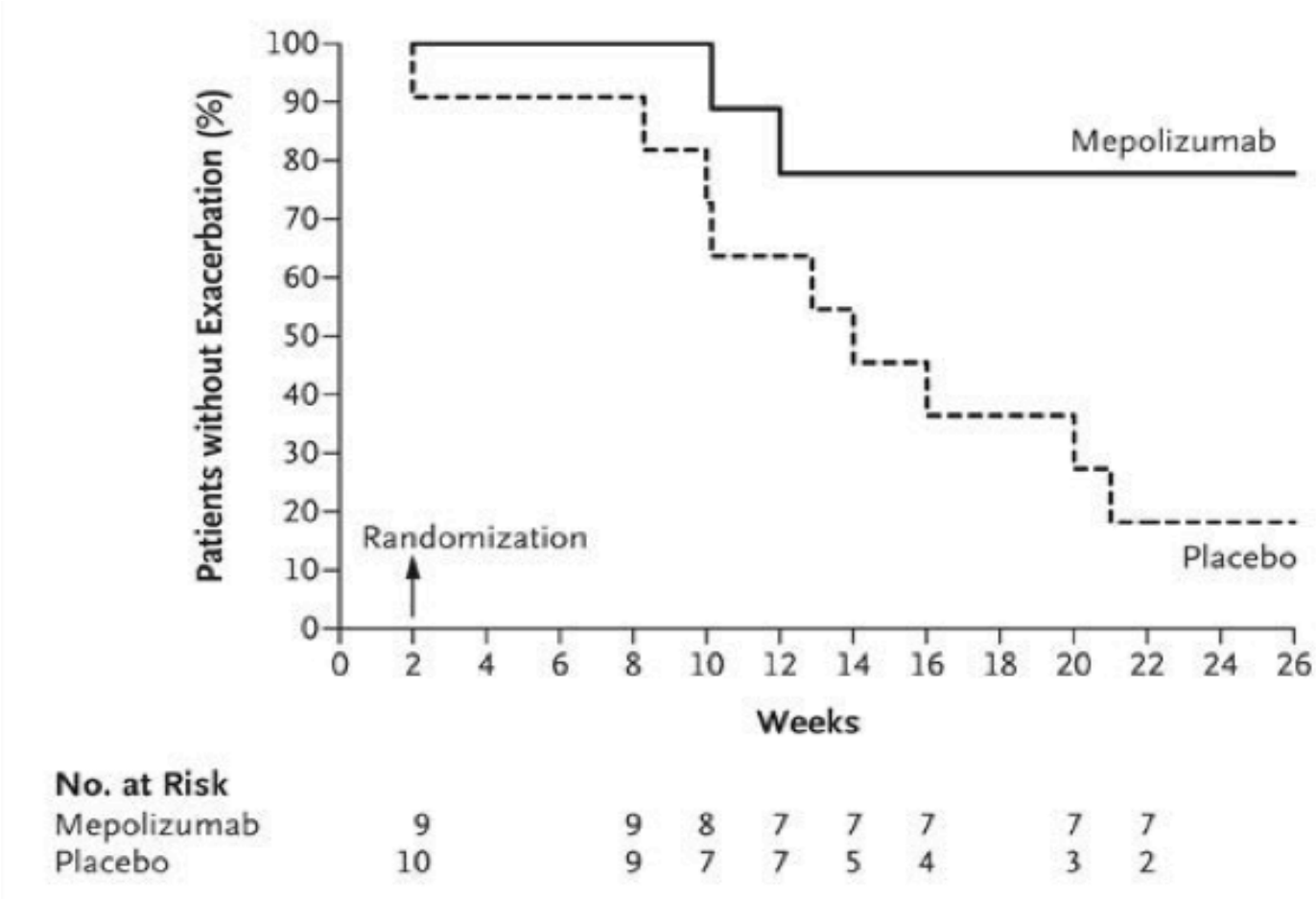
IL-5 is believed to be a key cytokine in eosinophil function at sites of allergic inflammation. A previous small dose-finding study found the humanized anti–IL-5 monoclonal antibody mepolizumab had no effect on allergen challenge in humans.

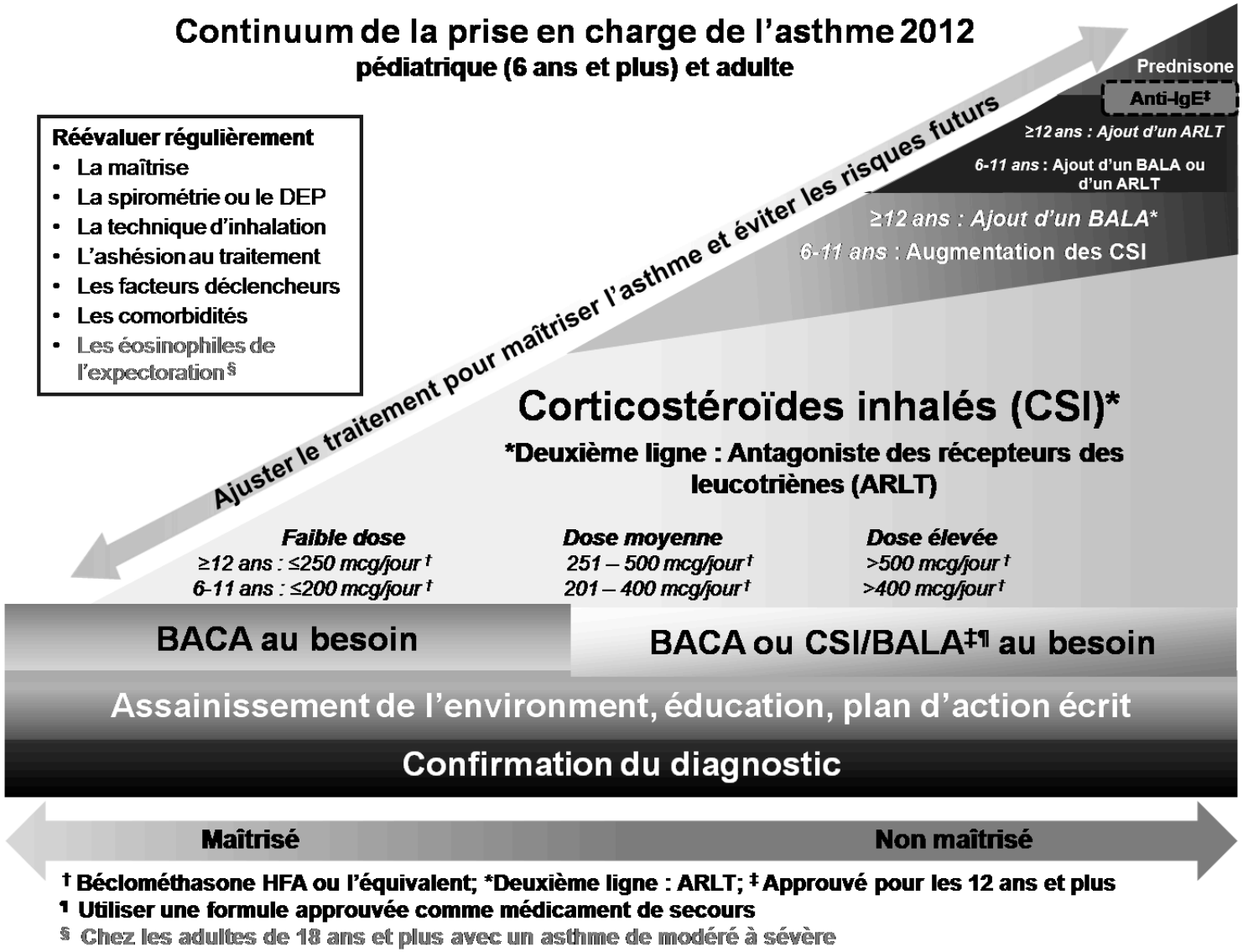
What This Study Adds to the Field

Mepolizumab treatment does not appear to add significant clinical benefit in patients with asthma with persistent symptoms despite inhaled corticosteroid therapy.

Mépolizumab et asthme sévère

Nair P et coll. N Engl J Med. 2009;360:985-93.





† Béclométhasone HFA ou l'équivalent; *Deuxième ligne : ARLT; ‡ Approuvé pour les 12 ans et plus

¶ Utiliser une formule approuvée comme médicament de secours

§ Chez les adultes de 18 ans et plus avec un asthme de modéré à sévère

Eur Respir J 2008; 32: 545–554
DOI: 10.1183/09031936.00155307

PERSPECTIVE

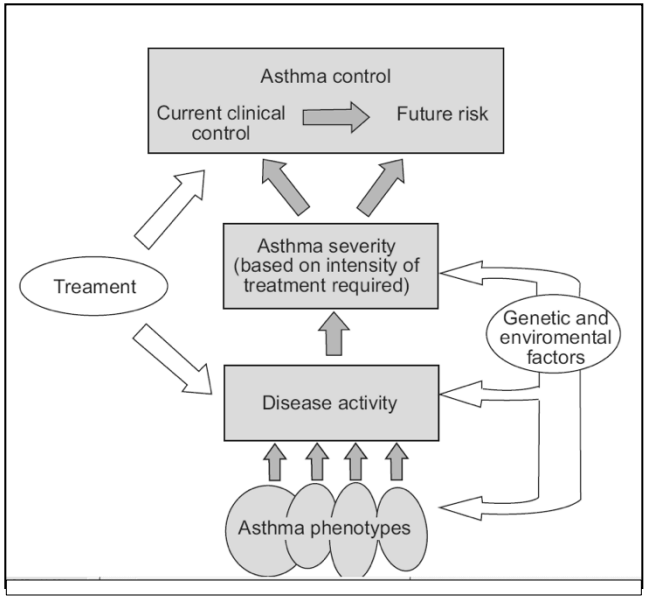
A new perspective on concepts of asthma severity and control

D.R. Taylor, E.D. Bateman, L-P. Boulet, H.A. Boushey, W.W. Busse, T.B. Casale, P. Chanez, P.L. Enright, P.G. Gibson, J.C. de Jongste, H.A.M. Kerstjens, S.C. Lazarus, M.L. Levy, P.M. O'Byrne, M.R. Partridge, I.D. Pavord, M.R. Sears, P.J. Sterk, S.W. Stoloff, S.J. Szefler, S.D. Sullivan, M.D. Thomas, S.E. Wenzel and H.K. Reddel

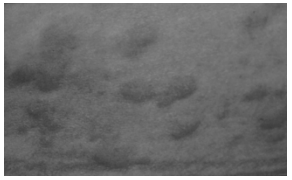
"

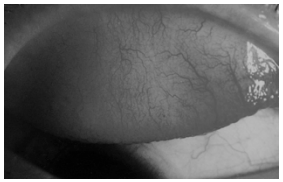
increasing awareness of heterogeneity of the underlying disease processes in asthma"

"These phenotypes may alter the intensity of the treatment required (severity) and, in turn, contribute to the patient's level of asthma control "



Asthme allergique vs non-allergique





Barnes CEA 2009

Similarities and differences between extrinsic (allergic) and extrinsic (non-allergic) asthma

	Extrinsic	Intrinsic
Clinical features		
Skin prick test	+	–
Age of onset	Usually early	Usually late
Genetics	Familial	Non-familial
Gender	Equal	Female preponderance
Exacerbations	URTI	URTI
	Allergens	–
Triggers	Allergen	–
	Exercise	Exercise
	Irritants	Irritants
Rhinitis	Common	Common
Nasal polyps	Rare	Common
Laboratory findings		
Specific IgE	↑	–
Total serum IgE	↑	↑ In 30%
Airway IgE (↑Cε, Iε)	↑	↑
Airway FcεRI+ve cells	↑	↑
Airway Th2 cells	↑	↑
Airway eosinophils	↑	↑
Th2 cytokines	↑	↑
Eosinophil chemokines	↑	↑
Macrophage IL-10, IL-12	↑	–
Autoantibodies	–	↑

Phénotypes de l'asthme
selon les différentes catégories phénotypiques

Phénotypes cliniques ou physiologiques, définis en fonction

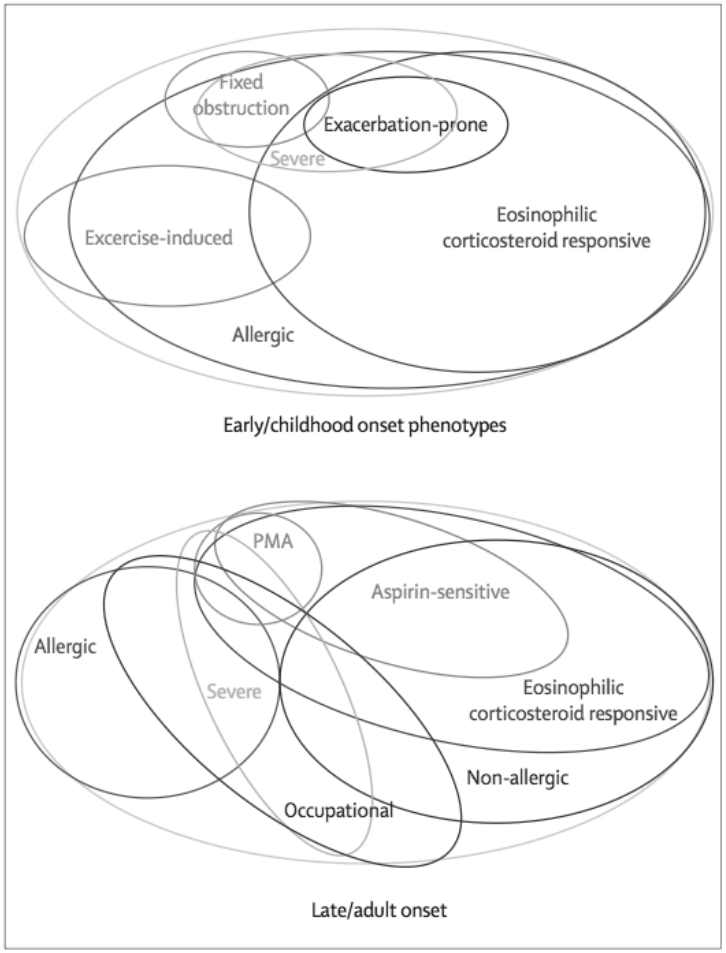
- De la sévérité
- Du nombre d'exacerbations
- De l'atteinte fonctionnelle
- De la résistance au traitement
- De l'âge de début

Phénotypes liés à des facteurs déclenchants

- Aspirine, AINS
- Allergènes environnementaux
- Allergènes ou irritants professionnels
- Menstruations
- Effort

Phénotypes inflammatoires

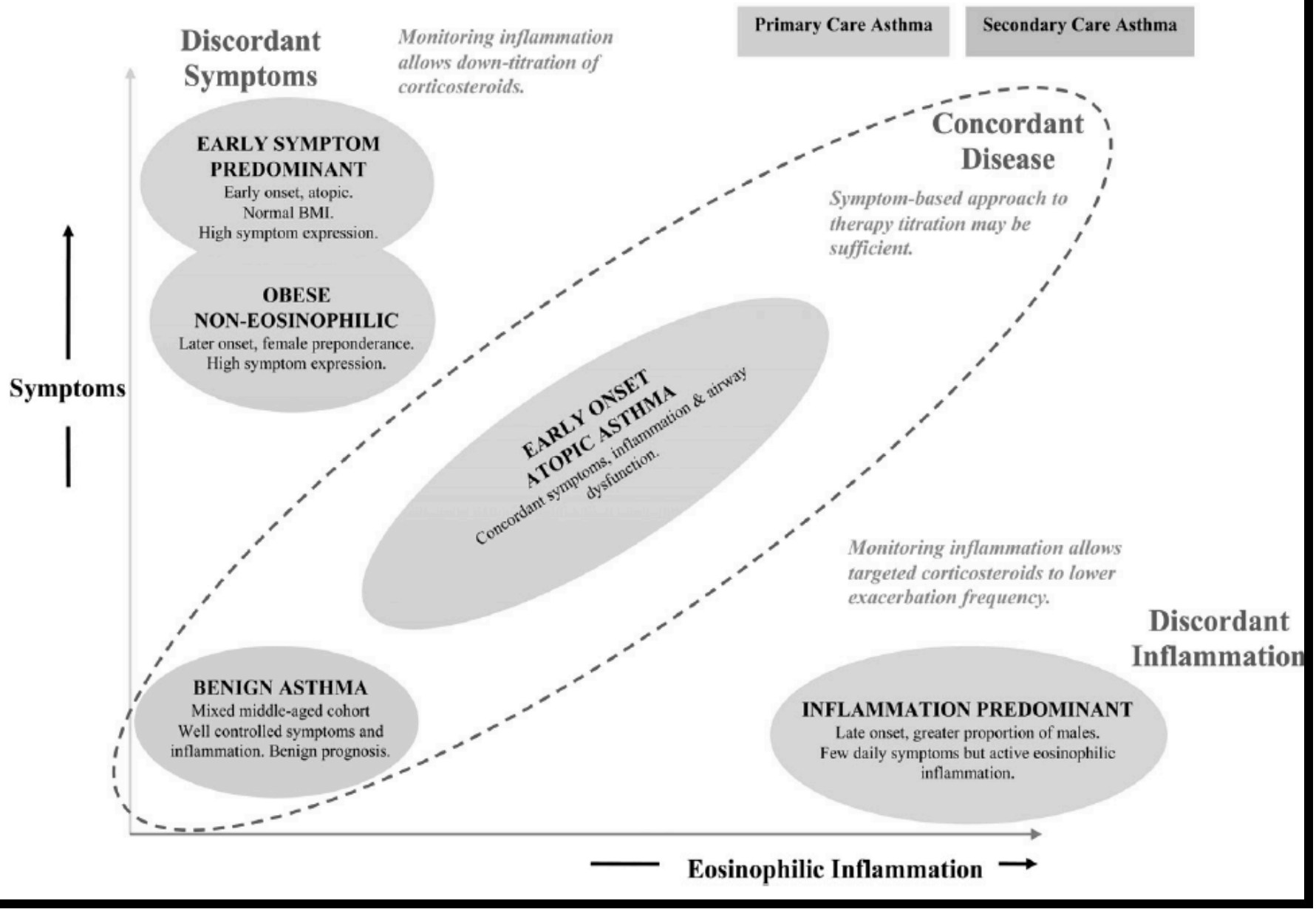
- Inflammation à éosinophiles
- Inflammation à neutrophiles
- Inflammation peu granulocytaire



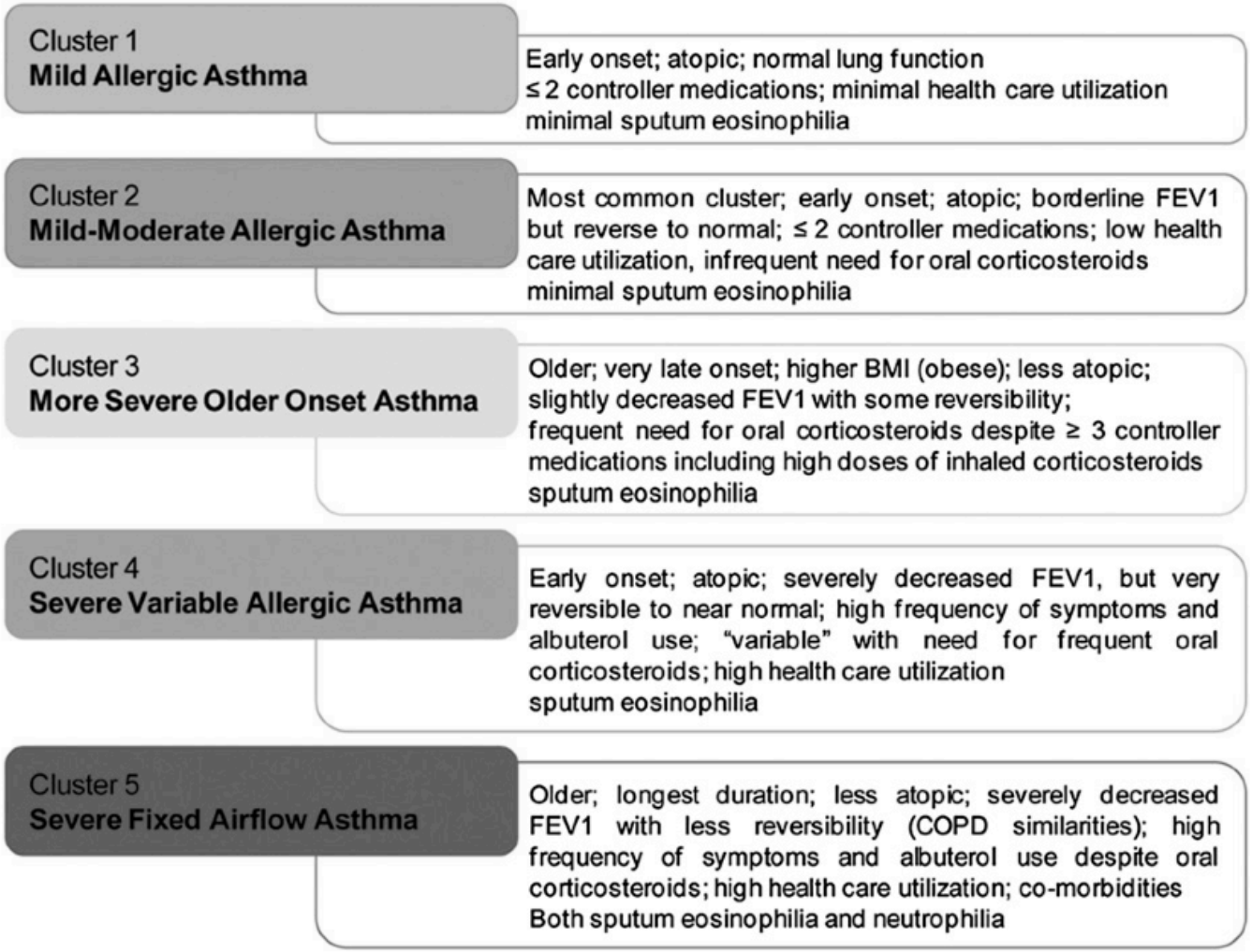
Wenzel Lancet 2006

Haldar, Pavord, Shaw, *et al.*: Clinical Asthma Phenotypes **AJRCCM 2008**

Heterogeneity in asthma expression

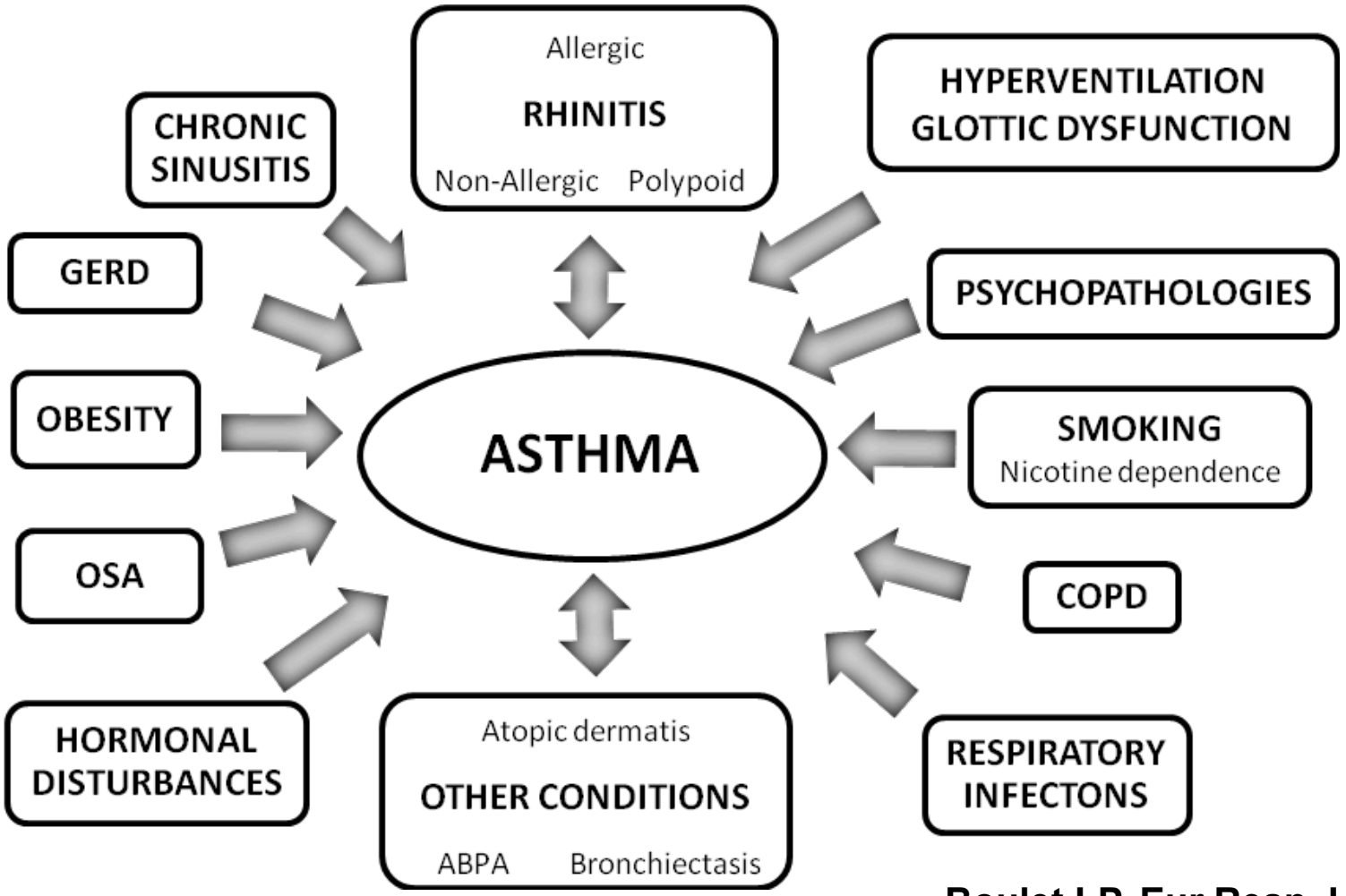


Analyse typologique « Cluster analysis » Asthme Sévère (Cohorte SARP-US)



Jarjour et al. AJRCCM 2012

Asthme et co-morbidités



Boulet LP. Eur Resp J 2009

Severe asthma: from characteristics to phenotypes to endotypes

S. Wenzel

Department of Medicine, Pulmonary, Allergy and Critical Care Medicine Division, Asthma Institute at UPMC/UPSOM, University of Pittsburgh, Pittsburgh, PA, USA

Clinical & Experimental Allergy

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E-mail: wenzelse@upmc.edu
Cite this as: S. Wenzel, *Clinical & Experimental Allergy*, 2012 (42) 650–658.

Abstract

Asthma, and severe asthma, in particular, is increasingly recognized as a heterogeneous disease. While traditional views of asthma have centered around a childhood onset disease with an allergic component, several large scale network studies are now confirming that severe asthma can present in multiple different ways, only 30–50% of which meet traditional childhood onset allergic criteria. To understand the different groups better, initial studies have attempted to define phenotypes of severe asthma. A phenotype is defined as the integration of different characteristics that are the product of the interaction of the patient's genes with the environment. Both clinical and statistical approaches have identified at least 3–5 phenotypes of severe asthma. However, these phenotypes, in isolation, do not identify the immunopathology that makes these clinical phenotypes distinct or identifies a target population for a specific approach to therapy. As biological characteristics are identified, phenotypes should continue to evolve towards asthma endotypes. The identification of these endotypes, either by matching biology, genetics and therapeutic responses to therapy with clinically or statistically defined phenotypes or through unbiased genetic and genomic approaches, remains limited. Moving forward, this integration of genetics, biology and clinical characteristics should substantially enhance our ability to effectively treat complex heterogeneous diseases, such as severe asthma.
Submitted 04 August 2011; revised 15 October 2011; accepted 16 November 2011

Endotypes associés à l'asthme sévère

	Natural history	Clinical	Genetics	Pathobiology	Biomarkers	Response to Rx
Early onset allergic	Childhood onset severe disease is persistent & probably progressive	Aeroallergen sensitivity other allergic diseases	17q12–21 Th2 pathway	Th2 cytokines, eos–less clear in severe disease	FeNO, increased specific IgE periostin	Mild responds to CSs/Th2 blockers. less clear in severe
Persistent eosinophilia	Adult onset, persistence and progression unknown	Often severe sinusitis, nasal polyps Subset with AERD	LT pathway HLA	Blood and lung eos despite CSs IL-5, cLT pathway	Sputum eos (not specific for this endo-type)	Anti-Th2/IL-5 LT modifiers
ABPM	Usually adult onset persistent, but progression unknown	Increased cough/ mucus central bronchiectasis	CFTR?	Blood and lung eos, mixed adaptive immunity	Fungus specific IgE and IgG	CSs, anti-fungals, possibly anti-IgE
Obese-Female	Very late onset persistence and progression unknown	Very symptomatic, but less airway obstruction and few severe exacerbations hormonal ties	Unknown	Inconsistent reports	Unknown	No good studies of targeted Rx, but poorly CS responsive
Neutrophilic	Unknown	Fixed airway obstruction, few other defined clinical characteristics	Unknown	Neutrophils, possibly increased innate immune activation	Unknown	Possible response to macrolide antibiotics

Wenzel Clin Exp Allergy 2012

Phénotype « asthme et obésité »

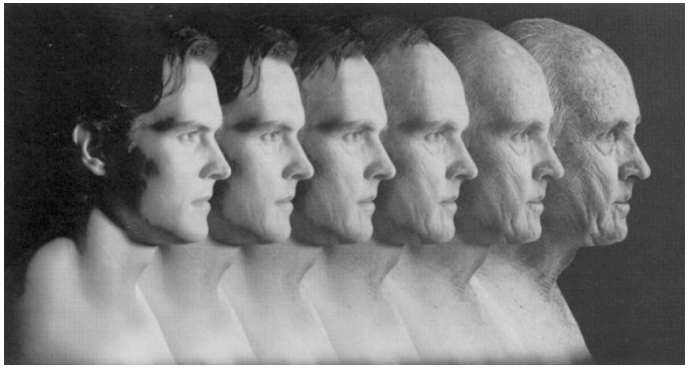
Etiologie:	génétique ? mécanique respiratoire ? aliments gras? inflammation systémique? multifactoriel
Présentation clinique:	prédomine chez la femme plus difficile à maîtriser co-morbidités fréquentes
Fonction pulmonaire:	VRE bas (respire à faibles volumes) travail respiratoire accru perte de l'effet protecteur de l'inspiration profonde
Inflammation broinchique:	moins éosinophilique inflammation systémique ++
Réponse au traitement:	réduite (CSI particulièrement)
Évolution clinique:	amélioration avec la perte de poids devenir à loing terme incertain

Phénotype de l'asthme chez le fumeur

Etiologie:	tabagisme
Présentation clinique:	à différencier de la MPOC/BPCO maîtrise plus difficile exacerbations plus fréquentes changements radiologiques (TDM) "COPD-like"
Fonction pulmonaire:	obstruction bronchique accrue et DCO abaissée perte accrue de fonction pulmonaire hyperinflation, perte de recul élastique
Inflammation broinchique:	plus neutrophilique expression accrue de l' arginase I & ODC dans les cellules épithéliales et le muscle lisse
Réponse au traitement:	réduite – réponse moindre aux CSI
Évolution clinique:	amélioration après cessation tabagique évolution vers la MPOC/BPCO

Phénotype de l'asthme chez la personne âgée

Etiologie:	le vieillissement !
Présentation clinique:	↑ morbidité & mortalité multiples problèmes (évaluation et traitement) ↑ exacerbations changements semblables à la MPOC/BPCO
Fonction pulmonaire:	↓ débits expiratoires, ↓ DCO hyperinflation, ↓ recul élastique
Inflammation bronchique:	plus neutrophilique
Réponse au traitement:	reduite ? Anti-cholinergiques?
Évolution clinique:	défavorable



Phénotype de l'asthme chez l'athlète

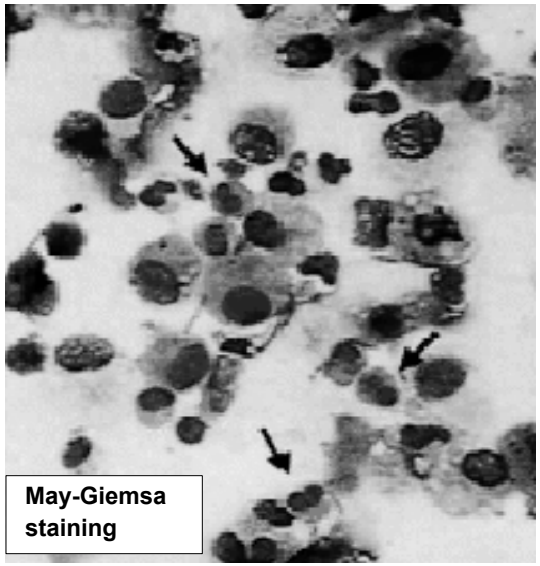
Etiologie:	exercice intense et répété, genetique ?
	expositions environnementales
Présentation clinique:	sous- et sur-diagnostic
	évaluation de la maîtrise difficile
	perception réduite de la bronchoconstriction ?
Fonction pulmonaire:	débits expiratoires supra-normaux
	réponse variable a la bronchoprovocation
Inflammation bronchique:	neutrophilique ou mixte
Réponse au traitement:	médications pour l'asthme bloquent le bronchospasme mais maîtrise difficile
Évolution clinique:	réversibilité des changements physiologiques et cliniques ?

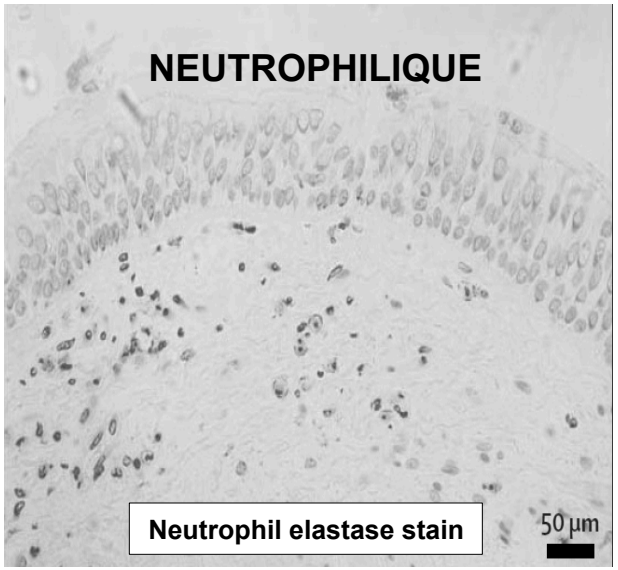
Pourquoi rechercher des biomarqueurs ?

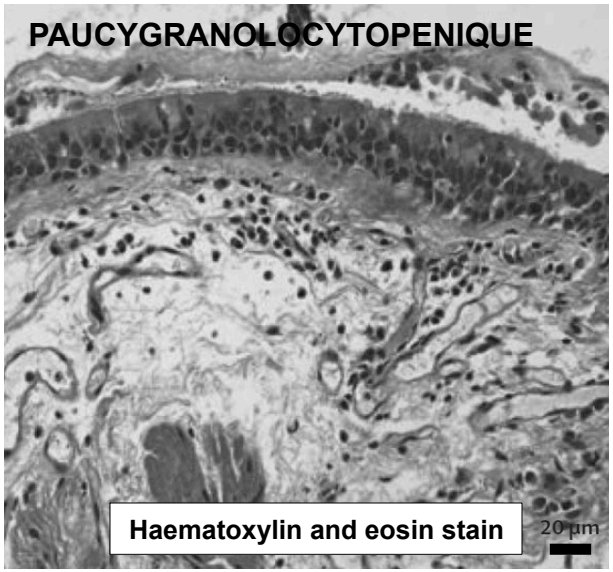
1. **Mieux définir les populations**
   d'un médicament particulier (pharmacogénétiques)
2. **Améliorer le développement de médicament**
   (pharmacocinétiques)
3. **Prédire l'évolution de la maladie** (justification de traitements prolongés ou plus intenses) (diagnostics et prognostics)
4. **Monitorer les effets d'un traitement** (pharmacodynamiques)
5. **Prédire le devenir clinique** (cible reflétant la maladie)
6. **Monitorer les effets secondaires** (biomarqueurs de sûreté)
7. **Identifier les nouvelles voies biologiques** impliquées dans la pathologie de la maladie

Adapté de Cazzola M & Novelli G. Pulm Pharmacol Ther 2010

Phénotypes inflammatoires de l'asthme







Allergènes
Agents sensibilisants
Réduction des stéroïdes
Autres

Infections virales et bactériennes
Tabagisme
Polluants atmosphériques
Athlète /obèse
Occupationnelle
Autres

Asthme résistant au CS ?
Hautes doses de CS ?
Autres

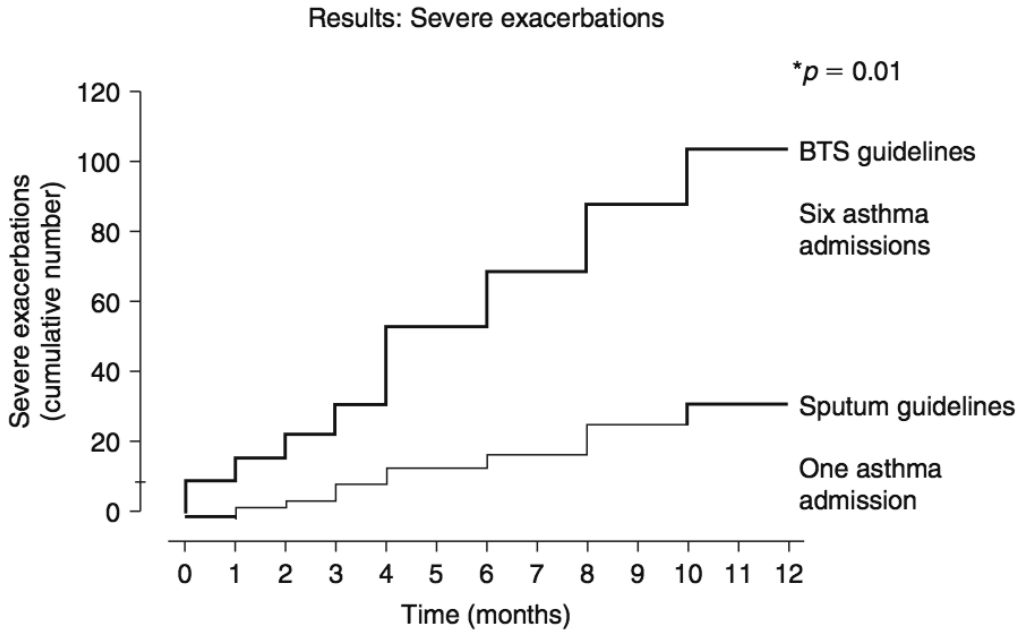
Evaluation of asthma control with induced sputum eosinophilia

Green et al Lancet 2002; 360: 1715-1721.

-
  modéré à sévère

- BTS Guidelines vs
  contrôle des éosinophiles

- Période de 12 mois



Exacerbations sévères Admissions

-

-

(p= 0.01) (p= 0.047)

Avantages des stratégies basées sur l'analyse de l'expectoration induite

- Diminue les exacerbations de l'asthme
- Améliore la fonction pulmonaire même dans l'asthme sévère
- Diminue le remodelage bronchique
- Diminue les exacerbations des BPCO
- Coût efficient

Phénotypage avec le NO Expiré (>35ppb)

- Plus grande réactivité bronchique (Réponse BD ou Métacholine)
- Plus forte éosinophilie bronchique
- Plus fréquence évidence d'atopie
- Plus d'hyperinflation
- Réduction de la perception des symptômes

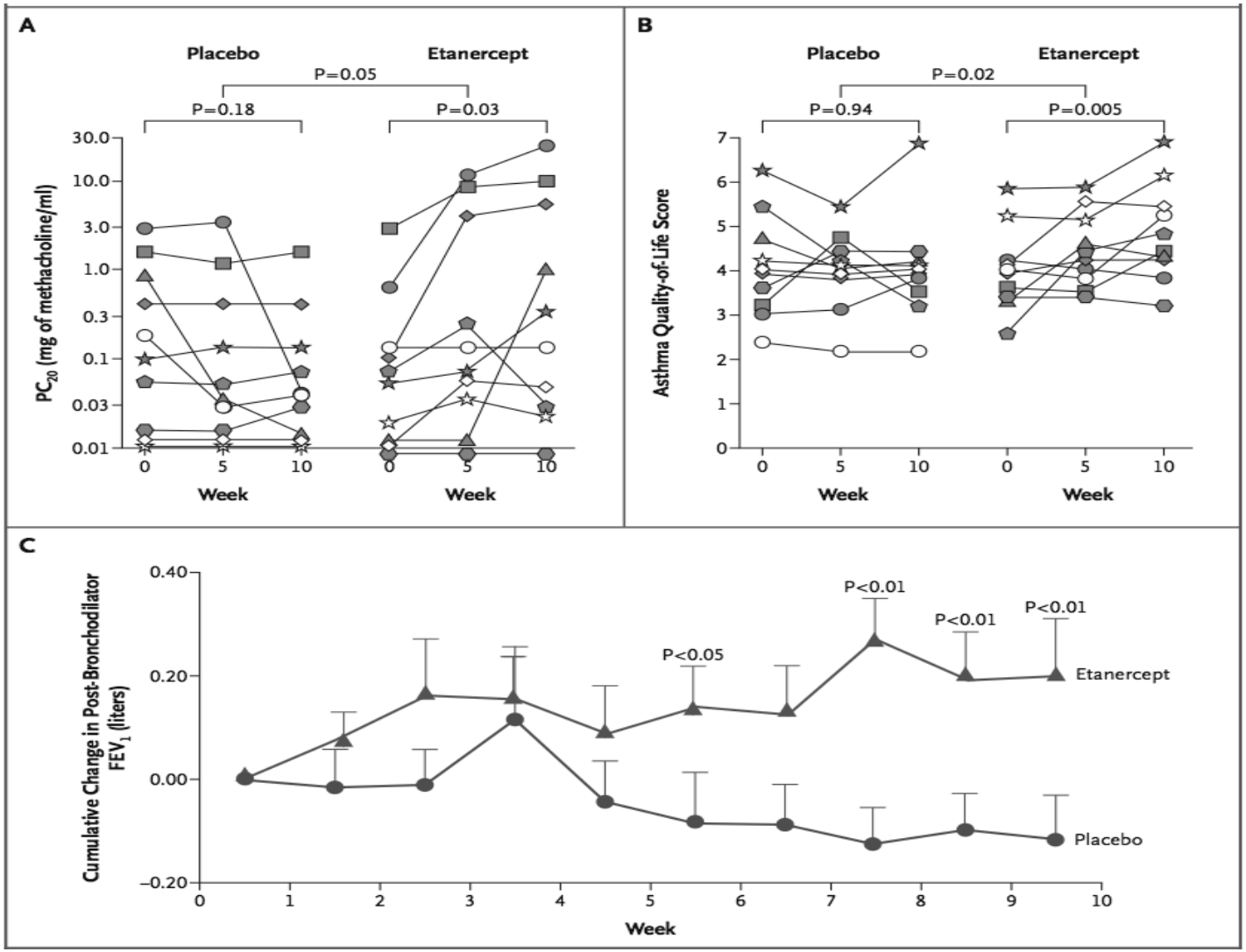
Pour l'asthme sévère

- Plus grand obstruction bronchique et hyperinflation
- Plus fréquente utilisation de soins d'urgence

Dweik et al. Use of FeNO measurement to identify a reactive, at risk phenotype among patients with asthma. Am J Respir Crit Care Med 2010;181:1033-1041

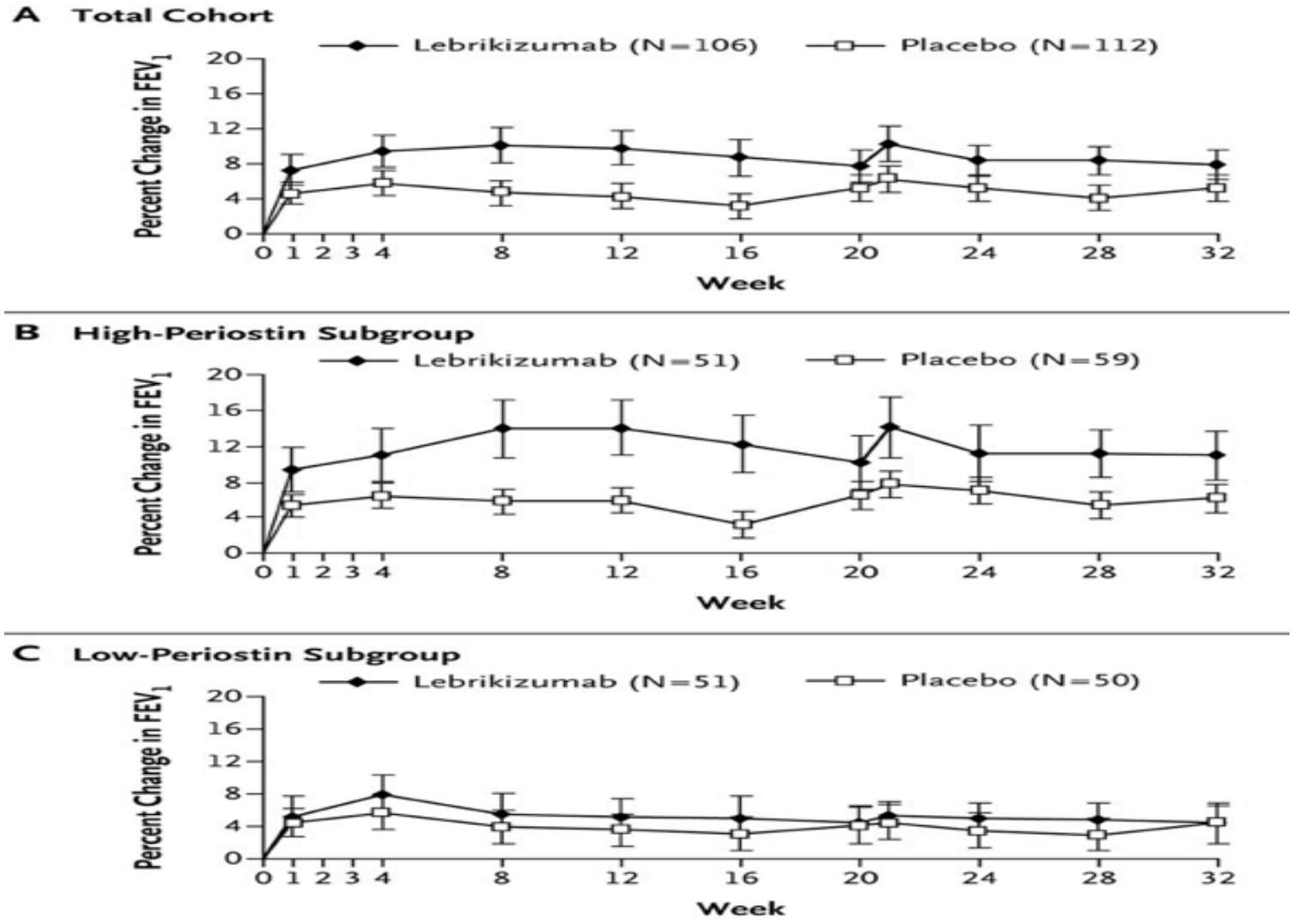
Evidence of a role of tumor necrosis factor alpha in refractory asthma

Berry et al NEJM 2006

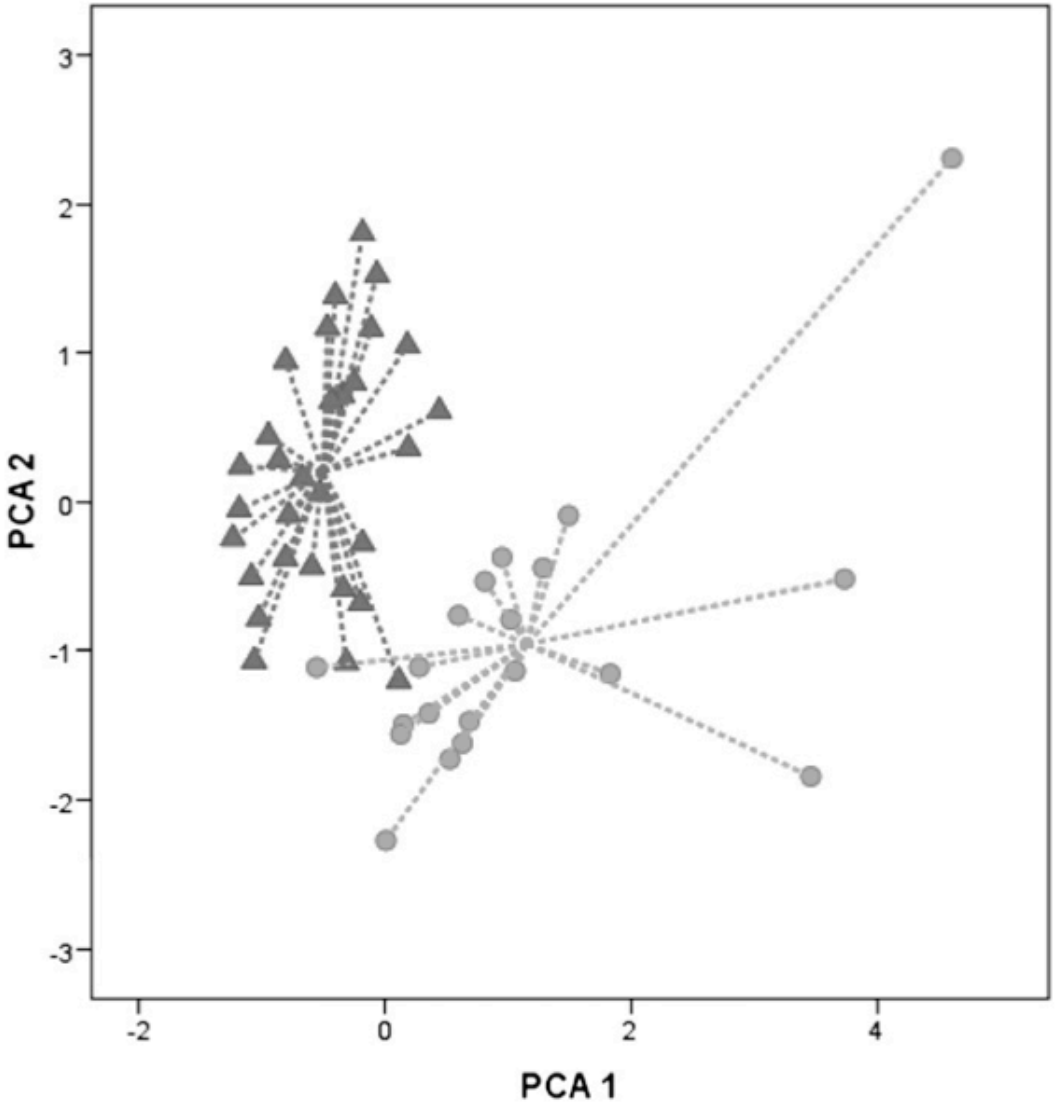


Librikizumab et asthme : la périostine comme marqueur de réponse

Corren J et coll. N Engl J Med. 2011;365:1088-98



Olfactométrie (Electronic Nose)



Two-dimensional principal component analysis (PCA) plot showing the discrimination of breathprints between patients with chronic obstructive pulmonary diseases (triangles) and patients with asthma (circles) along discriminative composite principal factors. Accuracy, 96%; P , 0.0001.

Fens et coll. AJRCCM 2009

CHEST Translating Basic Research Into Clinical Practice
2010

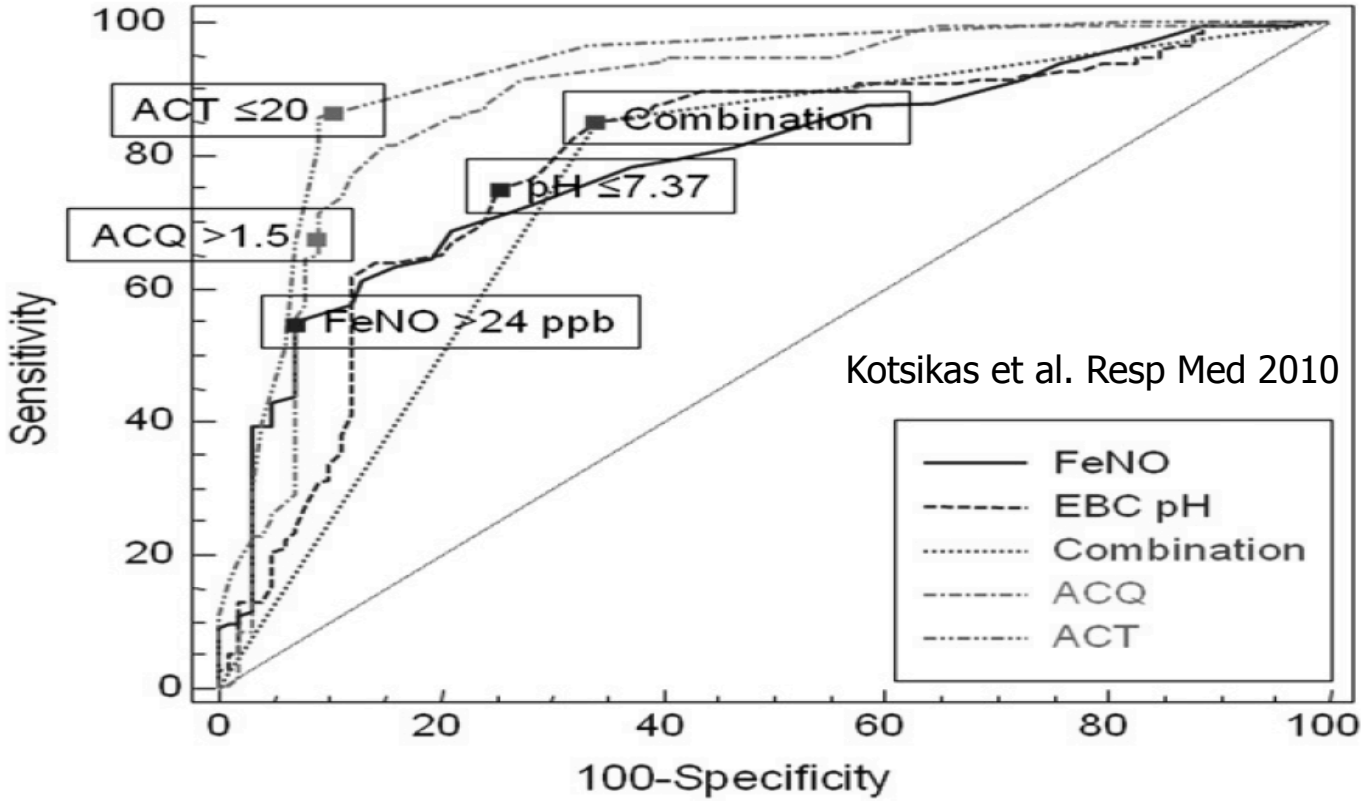
An Integrative Systems Biology Approach to Understanding Pulmonary Diseases

Charles Auffray, PhD; Ian M. Adcock, PhD; Kian Fan Chung, MD; Ratko Djukanovic, MD; Christophe Pison, MD, PhD; and Peter J. Sterk, MD, PhD

The pan-European project Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED), as part of the Innovative Medicines Initiative, will push this further by integrating high dimensional data from invasive (bronchial biopsies), non-invasive (blood, sputum, exhaled air) and patient-reported outcomes into distinct phenotype handprints by using an innovative systems biology approach.

This will enable more detailed phenotyping of adult and paediatric severe asthma and prediction of therapeutic efficacy in view of tailored management.

Associations de marqueurs?



Receiver operating characteristics (ROC) curves for FeNO, EBC pH and their combination in the identification of well-controlled asthma

Conclusions

- La recherche sur les biomarqueurs pourra faire progresser le diagnostic, le phénotypage et l'ajustement thérapeutique de maladies tels l'asthme et possiblement d'autres maladies respiratoires
- Peut aider à prédire le devenir clinique et guider la thérapie
- Peut établir les relations entre l'activité de la maladie et différents aspects clinico-pathologique
- Recherche sur de nouveaux biomarqueurs requise